Biaryl Synthesis

DOI: 10.1002/anie.200700064

Asymmetric Assembly of Aromatic Rings To Produce Tetra-*ortho*-Substituted Axially Chiral Biaryl Phosphorus Compounds**

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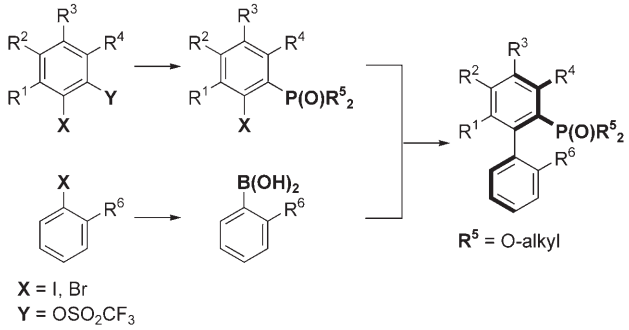
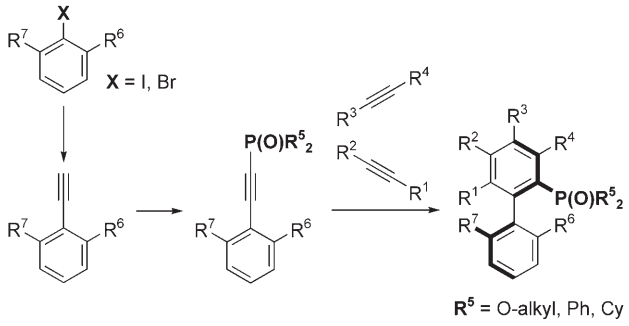
Axially chiral biaryl bisphosphine ligands have been employed widely in asymmetric catalysis, including in the industrial synthesis of chiral pharmaceuticals and perfumeries.[1] However, frequently bisphosphine ligands can not be used in transition-metal-catalyzed reactions, as they inhibit the desired catalytic cycles. To circumvent this limitation, Uozumi and Hayashi prepared a number of novel axially chiral biaryl monophosphine ligands,[2] which have since been applied in a wide variety of catalytic asymmetric reactions.[3]

An enantioselective synthesis of a tri-*ortho*-substituted axially chiral biaryl monophosphorus compound through palladium-catalyzed enantioposition-selective cross-coupling of an achiral symmetrical biaryl ditriflate with phenylmagnesium bromide followed by phosphorus introduction was developed by Hayashi et al.[4] A more straightforward route, a catalytic enantioselective aryl–aryl cross-coupling reaction,[5,6] was described by Yin and Buchwald (Scheme 1).[7] They developed a novel asymmetric Suzuki–Miyaura cross-coupling of phosphorus-containing aryl halides and aryl boronic acids; however, this method is restricted to the synthesis of sterically less demanding tri-*ortho*-substituted biaryl phosphonates.[7] The reaction conditions—elevated temperature (40–80 °C) and long reaction time (17–48 h)—and enantioselectivities (57–92 % *ee*) also left room for improvement. Hence, an efficient catalytic enantioselective method applicable to the asymmetric synthesis of tetra-*ortho*-substituted biaryl monophosphorus compounds with axial chirality that is thermally more stable toward racemization would be attractive.

Our research group first demonstrated that the combination of cationic rhodium(I) complexes with binap-type ligands (binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl) is extremely effective for catalytic inter- and intramolecular [2+2+2] cycloadditions.[8,9] Since this discovery, we have applied these catalysts in a number of chemo-, regio-, and enantioselective [2+2+2] cycloadditions,[10–12] including the synthesis of axially chiral compounds.[12–14] In our previous enantioselective synthesis of biaryl compounds, the use of electron-deficient and coordinating alkynes with carbonyl substituents was highly effective in furnishing axially chiral biaryl compounds with high *ee* values.[12] Although the coordination of carbonyl groups to the cationic rhodium center enabled high enantioselectivities, the high reactivity of alkynyl carbonyl compounds toward [2+2+2] homocycloaddition resulted in lowered yields of the desired [2+2+2] cross-cycloaddition products. To extend this methodology to the practical synthesis of axially chiral biaryl phosphorus compounds, we investigated the use of alkynyl phosphonates instead of alkynyl carbonyl compounds (Scheme 2).[15–17] In this new approach, the selective introduction of various substituents, including a phosphorus-centered functional



Scheme 1. Synthesis of tri-*ortho*-substituted axially chiral biaryl phosphonates through asymmetric aryl–aryl cross-coupling.



Scheme 2. Synthesis of tetra-*ortho*-substituted axially chiral biaryl phosphonates and phosphine oxides through the asymmetric assembly of aromatic rings. Cy = cyclohexyl.

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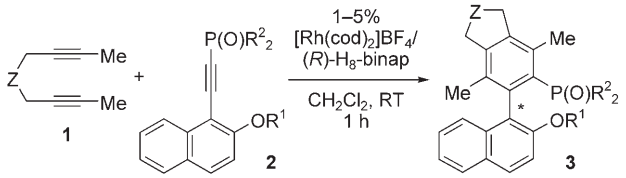
[**] This research was supported partly by the Japan Science and Technology Agency within the framework of the Collaborative Development of Innovative Seeds (potentiality verification stage). We thank Takasago International Corporation for the gift of H_8-binap.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

group, construction of a biaryl skeleton, and introduction of axial chirality would be possible in a single step. The reaction substrates, di-*ortho*-substituted arylethynyl phosphonates and phosphine oxides, can be prepared readily through the Sonogashira coupling of 2,6-disubstituted aryl halides with terminal alkynes followed by phosphinylation of the alkyne terminus. These two steps are not influenced by the steric bulk of the aryl group because of the sterically undemanding linear geometry of the alkyne. We envisaged that the electron-deficient and coordinating character of the phosphonyl moiety would enable high enantioselectivity, and that its steric bulk would hinder the [2+2+2] homocycloaddition.

We first investigated the asymmetric [2+2+2] cycloaddition with the readily prepared alkynyl phosphonate **2a** derived from 2-methoxynaphthalene. We were pleased to find that when a solution of the ether-linked diyne **1a** in CH_2Cl_2 was added dropwise over 20 min at room temperature to a solution in CH_2Cl_2 of **2a** and a cationic rhodium(I)/(*R*)-H_8-binap[18] complex (5 mol%), the tetra-*ortho*-substituted axially chiral biaryl phosphonate (−)-**3aa** was obtained in quantitative yield with excellent enantioselectivity (Table 1, entry 1). No reaction was observed upon the treatment of **2a** with the cationic rhodium(I)/(*R*)-H_8-binap complex, which confirms the excellent selectivity for the desired [2+2+2] cross-cycloaddition. Importantly, the use of (*S*)-H_8-binap as a ligand furnished the opposite enantiomer (Table 1, entry 2). Furthermore, as the catalytic activity of this rhodium catalyst is very high, the reaction can even be carried out in the presence of 1 mol% of the catalyst (Table 1, entry 3).

Table 1: Rh^I/H_8-binap-catalyzed enantioselective [2+2+2] cycloaddition of symmetrical 1,6-diynes with monoalkynes.



Entry	**1** (Z, equiv)	**2** (R^1, R^2)	Catalyst [mol%]	Yield [%][a]	*ee* [%]
1	**1a** (O, 1.5)	**2a** (Me, OEt)	5	>99	97 (−)
2[b]	**1a** (O 1.5)	**2a** (Me, OEt)	5	>99	95 (+)
3	**1a** (O, 1.5)	**2a** (Me, OEt)	1	>99	96 (−)
4	**1b** (CH_2, 1.5)	**2a** (Me, OEt)	5	>99	97 (−)
5	**1c** (NTs, 1.0)	**2a** (Me, OEt)	5	96	95 (+)
6	**1c** (NTs, 1.0)	**2b** (CH_2OMe, OEt)	5	99	98 (−)
7	**1c** (NTs, 1.0)	**2c** (Bn, OEt)	5	>99	97 (−)
8	**1a** (O, 1.5)	**2d** (Me, Ph)	5	92	91 (−)
9	**1b** (CH_2, 1.5)	**2d** (Me, Ph)	5	86	91 (−)
10	**1a** (O, 3.0)	**2e** (Me, Cy)	5	>99	95 (+)[d]
11	**1b** (CH_2, 3.0)	**2e** (Me, Cy)	5	70[c]	96 (+)

[a] Yield of the isolated product. [b] Ligand: (*S*)-H_8-binap. [c] 30% of **2** recovered. [d] *S* enantiomer. Bn = benzyl, cod = 1,5-cyclooctadiene, H_8-binap = 2,2′-bis(diphenylphosphanyl)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl, Ts = *p*-toluenesulfonyl.

We tested the generality of the reaction with regard to both cycloaddition partners. Not only the ether-linked diyne **1a**, but also the hydrocarbon-linked diyne **1b** (Table 1, entry 4) and the tosylamide **1c** (entry 5) were suitable substrates for this transformation. With respect to the substituent at the 2-position of the 1-alkynyl naphthalene, the methoxymethoxy and benzyloxy derivatives **2b** and **2c** were also suitable substrates for the reaction (Table 1, entries 6 and 7). Importantly, this method is not restricted to the synthesis of phosphonates. Both high yields and high enantioselectivities were observed when the sterically more demanding diphenylphosphine oxide **2d** and dicyclohexylphosphine oxide **2e** were employed (Table 1, entries 8–11).[19] The absolute configuration of the dicyclohexylphosphine oxide (+)-**3ae**, synthesized from **1a** and **2e**, was determined to be *S* by the anomalous dispersion method (Figure 1).[20]

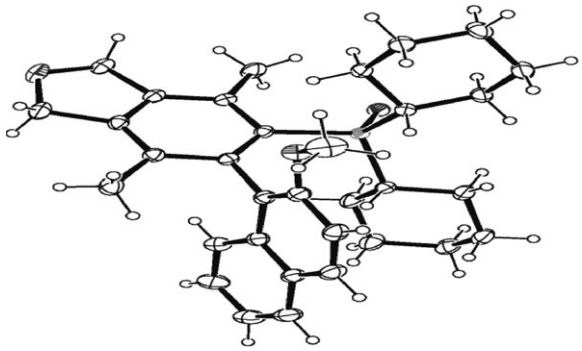
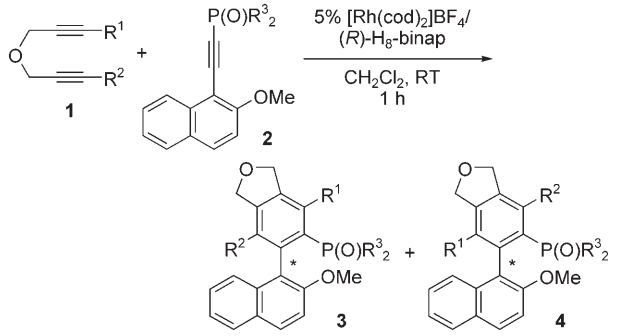


Figure 1. ORTEP diagram of (*S*)-(+)-**3ae** (product of Table 1, entry 10; R^1 = Me, R^2 = Cy, Z = O). C white, P gray, O black.

The asymmetric [2+2+2] cycloaddition was also applied to unsymmetrical diynes (Table 2). Diynes **1d** and **1e** with a phenyl group and a methyl group or a hydrogen atom at the alkyne termini reacted with **2a** and **2d** to give the corresponding biaryl compounds with high enantioselectivities as single regioisomers **3** (Table 2, entries 1–3). On the other hand, the diyne **1f** with a methyl group and a hydrogen atom at the alkyne termini reacted with **2a** and **2d** to give the corresponding biaryl compounds in quantitative yield as separable regioisomers **3** and **4** with good to high enantioselectivities (Table 2, entries 4 and 5). Importantly, remaining compound **2** could be recovered by chromatography on silica gel (Table 1, entry 10 and Table 2, entries 1–3).

The synthetic method described herein allows the preparation of a range of new axially chiral biaryl phosphorus compounds in which the aromatic ring bonded to the phosphorus atom is highly substituted. These biaryl compounds are not readily accessible by conventional asymmetric aryl–aryl cross-coupling approaches. Buchwald and co-workers reported recently that the substituents *ortho* to the phosphorus center of achiral biaryl monophosphines may lock the ligand into a certain conformation, which plays an important role in palladium-catalyzed cross-coupling reactions.[21] Hence, our new axially chiral biaryl phosphorus compounds may construct a rigid chiral environment and be applicable in a variety of catalytic asymmetric reactions. The industrial application of this asymmetric ring-assembly method to the synthesis of a wide variety of chiral mono-

Table 2: Rh^{I}/H_8-binap-catalyzed regio- and enantioselective [2+2+2] cycloaddition of unsymmetrical 1,6-diynes with monoalkynes.



Entry	**1** (R^1, R^2, equiv)	**2** (R^3)	Yield [%][a] **3**	**4**	*ee* [%] **3**	**4**
1	**1d** (Ph, Me, 1.5)	**2a** (OEt)	80[b]	<1	86 (−)	–
2	**1e** (Ph, H, 3.0)	**2a** (OEt)	73[c]	<1	96 (−)	–
3	**1e** (Ph, H, 3.0)	**2d** (Ph)	34[d]	<1	74 (−)	–
4	**1f** (Me, H, 1.5)	**2a** (OEt)	65	35	93 (+)	87 (−)
5	**1f** (Me, H, 3.0)	**2d** (Ph)	54	46	58 (−)	86 (−)

[a] Yield of the isolated product. [b] 20% of **2** recovered. [c] 27% of **2** recovered. [d] 66% of **2** recovered.

and bisphosphorus ligands may also be possible in view of the ready access to substrates, mild reaction conditions, operational simplicity, and high catalytic activities.

Experimental Section

Representative procedure (Table 1, entry 2): Under an Ar atmosphere, (*R*)-H_8-binap (6.3 mg, 0.010 mmol) and $[Rh(cod)_2]BF_4$ (4.1 mg, 0.010 mmol) were dissolved in CH_2Cl_2 (1.0 mL) in a Schlenk tube, and the solution was stirred at room temperature for 5 min. H_2 (1 atm) was introduced into the resulting solution, which was then stirred at room temperature for 1 h. The mixture was concentrated to dryness, the residue was redissolved in CH_2Cl_2 (0.4 mL), and a solution of **2a** (318.3 mg, 1.00 mmol) in CH_2Cl_2 (1.6 mL) was added. A solution of the diyne **1a** (183.2 mg, 1.50 mmol) in CH_2Cl_2 (3.0 mL) was then added dropwise over 20 min at room temperature, and the resulting mixture was stirred at room temperature for 1 h, then concentrated and purified by column chromatography on silica gel (hexane/EtOAc/Et_3N 3:1:1) to furnish (−)-**3aa** (439.6 mg, 1.00 mmol, >99% yield, 97% *ee*) as a colorless solid. M.p. 77.3–78.9 °C; $[\alpha]_D^{25} = -22.8°$ (c = 20.8, $CHCl_3$, 97% *ee*); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.87$ (d, J = 8.7 Hz, 1H), 7.82–7.74 (m, 1H), 7.35 (d, J = 9.3 Hz, 1H), 7.30–7.21 (m, 2H), 7.11–7.04 (m, 1H), 5.24 (s, 2H), 5.18 (s, 2H), 3.84 (s, 3H), 3.83–3.55 (m, 3H), 3.40–3.30 (m, 1H), 2.60 (s, 3H), 1.62 (s, 3H), 1.02 (t, J = 7.2 Hz, 3H), 0.85 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 153.1, 141.8, 141.7, 140.3, 140.1, 138.7, 138.5, 133.7, 133.5, 133.4, 128.8, 128.63, 128.55, 128.45, 128.4, 127.5, 126.0, 125.8, 124.2, 123.32, 123.27, 122.8, 112.5, 74.20, 74.17, 74.1, 60.73, 60.71, 60.66, 60.62, 55.8, 18.81, 18.76, 16.1, 15.8, 15.7, 15.6, 15.5 ppm; ^{31}P NMR ($CDCl_3$, 121 MHz): $\delta = 18.6$ ppm; IR (neat): $\tilde{\nu}$ = 3300, 2900, 1580, 1210, 1020, 960 cm^{-1}; HRMS (FAB): m/z calcd for $C_{25}H_{30}O_5P$: 441.1831 $[M+H]^+$; found: 441.1786; HPLC: chiralpak AD-H, hexane/2-PrOH 90:10, 1.0 mL min^{-1}, t_R: 8.56 min (major isomer) and 12.9 min (minor isomer).

Received: January 6, 2007
Published online: April 19, 2007

Keywords: alkynes · biaryls · cycloaddition · phosphorus · rhodium

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